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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,561	05/02/2002	Audrey Goddard	P3230R1C001-168	9766

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,561	GODDARD ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment to the specification and claims, declarations and petition filed 11-21-05 have been entered into the record. Claim 6 has been cancelled. Claims 1-5 are pending and under examiniation.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Change in Inventorship

Pursuant to the request under 37 C.F.R. §1.48(b) signed by a party set forth in §1.33(b) and the charging of the processing fee set forth in § 1.17(i), the following individuals have been removed as inventors: Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen and Colin K. Watanabe.

Objections/Rejections Withdrawn

The title and abstract of the invention are not descriptive of the now claimed invention is withdrawn in view of Applicants amendments.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at least at page 35 is withdrawn in view of Applicants amendments.

The use of the trademark ATCC™ has been noted in this application is withdrawn in view of Applicants amendments.

The objection of claims 1-6 because of the following informalities: the claims improperly reference Figures is withdrawn in view of Applicants amendments.

The rejection of Claims 1 and 6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants amendments.

Rejections Maintained

Priority

Applicants argue that the data in Example 18 (tumor versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8-24-00 and as such this application is at least entitled to the filing date of 8-24-00 for the utility of differential normal and tissue expression. This is not persuasive, the priority document does not comply with 35 USC § 120, utility and enablement for reasons set forth in the previous office action of record and reasons set forth herein. This relied upon utility is not a substantial utility for reasons made of record and argued herein.

Claims 1-5 stand rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by a specific, substantial and credible utility or, in the alternative a well-established utility is maintained for reasons made of record in the Office Action mailed 8-23-05.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the requirement for a substantial utility defines a "real world use" and cite *Brenner v Manson*, 383 US 519,534(1996) already of record. Applicants argue that MPEP 2107.01 that states that office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulation to mean that products or services based on the claimed invention must be "currently" available to the public. This is not persuasive, the rejection set forth did not require "current public availability", but a specific and substantial utility for the now claimed invention. Applicants argue that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial utility". This is not persuasive, the relied upon utility (increased

nucleic acid levels in normal tissue as compared to compared to tumor) specifically requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use and as such is therefore not a "substantial utility" (see MPEP 2107.01(1)). Applicants argue that the USPTO must establish that it is more likely than not that one of skill the art would doubt the truth of the statement of utility, namely that the gene encoding the polypeptide is differentially expressed in certain cancers compared to normal tissue and useful as a diagnostic tool and that one of ordinary skill in the art would reasonably doubt the asserted utility. This argument has been fully considered, but is not persuasive. Utility requires that the skilled artisan be able to use the claimed invention. The specification does not provide a specific and substantial or a well-established use. Applicants have provided a single analysis of nucleic acid without any relative range for basing a utility of alleged over-expression for the claimed protein(s) in normal tissue. There is no guidance on how to use this information for protein levels and therefore also no information on how to use the antibody to bind the polypeptide for diagnostic purposes. No levels (relative or absolute) of the claimed polypeptide are particularly disclosed. Applicants argue that if the gene is differentially expressed in cancer versus non-cancer tissue, then its mRNA and encoded polypeptide and antibody that binds the polypeptide are useful as diagnostics. This argument is pertinent to the instant claims because of the functional of the antibody would be to detect a polypeptide encoded by a nucleic acid that is over expressed in normal tissue as compared to melanoma. The argument has been fully considered, but is not persuasive. If one cannot use the encoding nucleic acid as a diagnostic tool for tumors, then one cannot use the encoded polypeptide either. Additionally, there is no data regarding protein expression in any tumor as compared to the control in the specification and Applicants are attempting to rely upon a correlation of increased mRNA levels of SEQ ID NO:37 with increased protein levels (SEQ ID NO:38). Applicants argue that the standard for utility is not a mater of statistical certainty, but more likely than not and reasonable probability.

Applicants again rely on an asserted reasonable probability of the correlation of mRNA levels with protein levels. This again is not persuasive, the record establishes that one skilled in the cancer diagnostic art would not find it "more likely than not" that the mRNA levels correspond with the protein levels, see Haynes et al, Pennica et al, Gokman-Polar et al and Lewin et al. Applicants argue the court holdings in *Fujikawa v. Wattanasin*, 93 F3d. 1559, 39 USPQ 2d 1985 (Fed. Cir. 1996) and *Cross v Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985) that indicate that when the *in vitro* results are general predictable of *in vivo* results establishes a significant probability that in vivo testing for the particular pharmacological activity will be successful. This is not persuasive, there is no claimed pharmaceutical composition and the issue is not correlation of in vitro data with in vivo results. The issue is solely *in vitro*, and the lack of reasonable correlation between mRNA levels and protein levels *in vitro*. In contrast to *Fujikawa v. Wattanasin*, 93 F3d. 1559, 39 USPQ 2d 1985 (Fed. Cir. 1996) and *Cross v Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985) this specification does not teach *in vitro* data for the protein. No levels of the protein are taught, absolute or not. Applicants review the record and indicate that their rebuttal evidence establishes the "more likely than not" standard for utility. Applicants argue Hu et al does not teach that indicate that a lack of correaltion means that genes with a less than five fold change in level of expression in cancer cannot serve as a molecuer markers of cancer. Hu et al was cited to provide evidence that one skilled in the art would not more likely than not believe that a change less than five fold would be indicative of a role in cancer as it related to the allegations of utility with respect to therapeutics and gene therapy. In order to have utility for therapeutic purpose or be useful in gene therapy, there must be some correlation with known or disclosed biological activity. The position of the office is that the art of record indicates that there is no reasonable correlation and that the allegation of utility based upon therapeutics is not specific and substantial. Applicants argue that they have established that the gene encoding the PRO polypeptide is differentially expressed and thus rely again on the

"reasonable correlation" of mRNA expression with protein expression. This again is not persuasive Haynes et al. is cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as **40-fold** or even **50-fold** were not uncommon (pg. 1863) and specifically teach "These results suggests that even for a population of genes predicted to be relatively homogenous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of corresponding mRNA transcript." (page 1863, column 1, section 2.1). Haynes et al teaches "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts. " (see page 1870, column 1, Concluding Remarks). Therefore, the skilled artisan immediately recognizes that, at the time of the invention, that no direct correlation between gene amplification/mRNA levels and increased polypeptide levels exists, no dogma exists between mRNA and polypeptide levels (for which neither are disclosed within the instant specification for PRO1411).

Applicants point to the Declaration of Dr. Grimaldi that clarifies the use of pooled samples. This again not persuasive, it does not establish the particulars of individual variation and statistical significance of individual variation. Diagnostic assays do not use pooled samples. Further, no evidence is proffered to support the opinion that the use of pooled samples "is more likely to be accurate than data obtained from a single individual". Applicants note that many protein based diagnostics in the art in which the level of a particular protein is assessed to determine whether a patient is suffer from a particular condition do not require a normal sample because initially a normal range of protein levels are defined and the patient sample is quantitated to determine whether it is outside of the normal range. This is not persuasive, this specification does not define a normal range for the claimed PRO polypeptide or any variant thereof. Pooled samples do not establish a normal range, they are a single data point. Range is established using multiple samples and

this specification lacks any statistical analysis of range for either the nucleic acid or corresponding protein. Applicants argue that the semi quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over-espressed or under expresses in tumor versus normal tissue. Mr. Grimaldi declares that the results of Example 18 reflect at least a 2-told difference in cDNA between tumor and normal counterpart. It is noted that the details of the semi-quantitative analysis described by Declarant Grimaldi are not detailed in the specification as filed nor is the "at least 2 fold difference" of the declaration. The specification only teaches "more highly" and does not indicate that "more highly" is at least a 2-fold difference. Applicants Exhibit 1 with respect to the visibility of a two fold difference in DNA mass using ethidium bromide staining is noted and provides evidence that an at least 2 fold difference can be observed for 61 ng and 124 ng DNA. However, the declaration remains not persuasive, because the cutoff of the assay as at least 2-fold is not established in the specification as filed for "more highly expressed". So while a 2-fold may be able to be observed, the specificaiton does not establish this as the criteria used at the time of filing. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See *Ex parte Simpson*, 61 USPQ2d 1009 (BPAI 2001), *Cf. Redac Int'l. Ltd. v. Lotus Development Corp.*, 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), *Paragon Podiatry Lab., Inc. v. KLM Lab., Inc.*, 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). 1) In the instant case, the nature of the fact sought to be established is whether or not the more highly expressed for mRNA provides meaningful results with respect to mRNA protein levels. The declaration of Dr. Grimaldi does not teach the level of reproducibility or the level of reliability of the results. There are no relative or absolute levels of polypeptide in control or tumor tissue disclosed. Neither the specification nor the declarations provide any evidence that indicates what the

differences were or if they were statistically significant. If a clinician took a lung tissue sample from a patient with lung cancer, for example, what is the likelihood that when compared with normal tissue, the level of PRO polypeptide from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? Applicants argue that the precise levels of gene expression are irrelevant, merely that they levels of tumor and normal are different. This is not persuasive. The differences have to be reproducible and statistically significant for use as an asserted diagnostic and moreover, the levels are extremely important as it relates to the correlation of mRNA with protein expression. As previously set forth, given the evidence presented by Haynes et al, Gokman-Polar et al and Lewin, it is clear that one skilled in the art would not assume that a small increase/decrease in mRNA would correlate with corresponding changes in polypeptide levels. In view of the totality of the evidence of record, one skilled in the art would not assume that gene expression (mRNA) necessarily parallels or is predictive of protein expression and would have to perform further experimentation to verify or rule it out. As such, this further experimentation indicates that the asserted utility is not "substantial". It is noted that the cited literature supports the position of a lack of correlation of gene amplification, mRNA levels and protein expression and specifically cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Nevertheless, gene amplification , is not equivalent to gene expression (i.e., mRNA), which is not the same as polypeptide data (i.e., as claimed). Applicants argue that they have established that it is the accepted understanding in the art that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. This specification does not teach the expression level of the claimed protein, nor is it demonstrated scientifically statistically significant. The means and methods of sample collection and specifics with respect to data analysis are not set forth in the specification as filed. Therefore, the art indicates

that it is not the norm that increased/decreased gene transcription results in increased/decreased polypeptide levels and the asserted utility of the PRO polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. The need for further research to reasonably identify or confirm a utility is not "substantial" because it does not identify a "real world" utility (MPEP 2107.01(1)). Applicants argue that a cursory inspection of Figure 1 of Haynes et al shows a clear correlation between the mRNA levels and protein levels measured. This is not persuasive, it contradicts the conclusions of the authors that specifically state "no strong correlation between protein and transcript levels" (page 1871, column 1, section 2.1). Applicants indicated that Haynes et al does not teach the absence of such a correlation. This is not persuasive Haynes et al teach "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts." Haynes et al is cited to specifically teach, at the time the invention was made, one of skill in the art would not have reasonably believed to the argued standard "more likely than not" that protein levels were increased as alleged. Applicants argue that the 50 fold variation of Haynes does not establish that the correlation is not "more likely than not". This is not persuasive, it was cited to demonstrate even given a very large variation that the protein levels do not reasonably predictably follow. The variation is huge, and according to the declarations the alleged observed difference in nucleic acid was at least 2-fold. Haynes et al specifically caution about drawing conclusions of protein levels based on transcript levels... indicating that there is no strong correlation. The art specifically teaches that the findings for yeast are also present in humans. Anderson et al teach that "Despite extensive work on the regulation of many individual genes, little attention appears to have been paid to the global question of the relation between mRNA and corresponding cellular protein abundances.." (Anderson et al , Electrophoresis, 18:533-537, 1997; see page 536, column

2.). Anderson et al teach that the correlation is 0.48 and indicates that the two major phages of gene expression regulation are of approximately equal importance in determining the net output of protein. Reanalysis of the data of Kawamoto et al, indicates that the correlation is coefficient is poor when one gene product, well separated from the gene cluster is omitted from the calculation (Anderson et al page 536, column 2, first full paragraph). Further, the lack of correlation between mRNA levels and protein levels in cancer is demonstrated by Chen et al (Molecular and Cellular Proteomics, 1:304-313, April 2002). Chen et al indicate that "Using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, we showed that only a subset of the proteins exhibited a significant correlation with mRNA abundance." (see Chen et al page 304, column 1, abstract). The specification does not indicate that the polyeptide of SEQ ID NO:52 belongs to this subset. As such, not all cancer proteins have a correlation and therefore, in the absence of any specific evidence to the contrary with respect to the polypeptide or antibodies that bind them, there is reason to doubt the asserted truth of the assertion of utility for the claimed antibodies as a diagnostic tool. Applicants argue that Chen et al and Anderson et al are not relevant because they use averages and tissues at different stages of disease and different normal tissue and also provide support for Applicants position. Applicants argue that the teaches of Chen could be a result of a lack of substantial shanges in mRNA level are speculative and does not change the conclusions articulated by Chen et al. There is no indication that the tumors and normal sample was taken either from the same individual or represented the same stage of tumor in this specification. Further, the comparison of the specification is a best a single assay and therefore no statistical relationship to the population has been established. All of Applicants arguments with respect to the deficiencies of Chen et al and Anderson et al are similarly present in the specification. A single analysis of a single sample was performed, there is no indication of type and stage of the tumor, there is too few normal samples obtained, there is no finding for individuals in a population and only an average. All of the

failings in the art are found in the specificaiton. It is easy find fault with published data, but the specification teaches a mere fraction of what is found in the art and does not obviate that the levels of mRNA reflect similar and statistically significant changes such that the claimed antibody could be used to diagnose tumor. The art provides at least an attempt to correlate mRNA and protein levels. The conclusions of Chen et al and Anderson et al teach that any random protein there is no more likely than not or reasonable expectation that the mRNA levels correlate with the polypeptide levels. Here, the specification provides none. Applicants argue that Chen et al is deficient because it did not determine differences in polypeptide in normal and diseased. Therefore, the skilled artisan immediately recognizes that, at the time of the invention, that no direct correlation between gene amplification/mRNA levels and increased polypeptide levels necessarily exists, no dogma exists between mRNA and polypeptide levels (for which neither are disclosed within the instant specification for polypeptide) and the state of the art at the time of filing provided reason to doubt the asserted truth of the specification. The examiner has considered the evidence of record and not found it to be persuasive, the cases are not rare as asserted by Applicants. Where systematic study was performed the presumed correlation was not, more likely than not, present. Therefore, the skilled artisan immediately recognizes that, at the time of the invention, no dogma exists between mRNA and polypeptide levels (for which neither are disclosed within the instant specification for PRO polypeptide). This is in fact defeats the assertion that there is a strong correlation by Applicants (i.e. "more likely than not"). Applicants have not presented any declaratory or other evidence establishing the correlation of levels for the mRNA of SEQ ID NO:51 and the protein levels of SEQ ID NO:52 *in vitro*. Applicants argue that the variability of Haynes et al is due to variability of measuring low levels of mRNA. This is not persuasive, Gygi et al specifically teach "the correlation between mRNA levels and protein levels was insufficient to predict protein expression levels from quantitative mRNA data" (see page 1720, abstract). Applicants argue that the need for quantitative data is irrelevant since it

is the differential expression that is important. Given the single assay of Applicant in Example 18, how is the skilled artisan able to predictably diagnose using the antibody to bind the polypeptide. Is the difference real if the assays are so variable ? Without multiple independent samples and levels it is impossible to ascertain any variability in the instant assay. Since the levels of the mRNA are not reported in the specification it is impossible for the skilled artisan to ascertain any variability that would apply to the instant case. However, given the known variability, the lack of teaching of inter-sample and inter-assay variability in the specification, the single point assay, it is impossible to reaonably conclude protein levels from mRNA levels. Further, Gygi et al teach that "We therefore expect that the correlation for all yeast proteins or for random selection would be less than 0.4" Less than 0.4 is less than "more likely than not". Further, Gygi et al indicate that "The observed level of correlation between mRNA and protein expression levels suggests the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translation control (15) and control of protein half-life (33). Since these mechanisms are also active in higher eukaryotic cells, we speculate that the is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells. " Gygi et al acknowledge potential issues with respect to measurements in both the mRNA and protein of the report. However, the conclusions remain the same. The declaration of Dr. Polakis has been considered but is not persuasive in view of Haynes et al, Gygi et al, Chen et al and Anderson et al of record as discussed *supra*. Applicants argue that Haynes et al teach that the art either implicitly or explicitly assume that for specific genes the transcript levels are predictive of protein levels. The teachings of Gygi et al indicate that this assumption is for any random polypeptide the correlation likely approximates 0.4 (less than the 0.51, more likely than not standard). Since, the absolute levels of Applicants mRNA and protein are not established it is not clear what category that they fall. Nonetheless, Haynes et al and Gygi et al clearly establish that the assumption of the art not predictable. Applicants argue that Lewin et al

teaches that that the overwhelming majority of regulatory events occur at initiation of transcription. That is the regulatory events in gene transcription not in protein expression. The issue here is protein levels. Applicants argue that Gokman-Polar et al, in contrast to the position of the office, teaches a general trend the mRNA levels predict protein levels. This is not persuasive, Gokman-Polar et al concludes "the small alterations in mRNA expression for these PKC isoenzymes do not correlation with the dramatic changes in expression of the corresponding protein." (page 1378, column 2). Thus, the conclusions of Gokman-Polar are contrary to Applicants position. Further, the data at page 1379, Figure 6 and 7 show an apparent at least two fold difference in QRT-PCR products, does not correspond to similar difference is protein production. A "trend" is not established and indicates that visible fold differences in PCR-products do not correlate with the corresponding measured protein level. Applicants argue Pennica et al and Konopka et al are not relevant to the instant case. This is not persuasive, all the references address the alleged dogma of the art gene copy number = mRNA copy number = protein copy number. Pennica and Konopka et al were cited to teach that gene copy number = mRNA copy number to dispute alleged dogma of the art from all its perspectives for completeness of the record. Hu et al was cited to teach that a correlation with disease causality is not established with differences less than 10-fold differences in mRNA expression. This is important to the instant asserted utilities because, the specification specifically indicated that one of the utilities was to use the protein as a therapeutic. In order to use a protein as a therapeutic it must have some established relationship to tumor formation or lack thereof. In this case, since the specification is devoid of absolute levels of mRNA or protein, Hu et al was used to indicate that mere alleged 2-fold increase in mRNA does not establish a role for the protein in tumor formation. Applicants' response focuses on the use of the mRNA and protein for diagnostic purposes and appears to have abandoned this asserted therapeutic utility in the specification. Applicants also assert the second opinion declaration of Dr. Grimaldi, that those who work in this field are well

aware in the vast majority of cases, when a gene is over-expressed... the gene product or polypeptide will also be overexpressed and this same principle applies to underexpression. This again is not persuasive, it is an opinion that is specifically rebutted by Haynes et al and Gygi et al of record. The declaration of Dr Polakis is contrary to the conclusions of Haynes et al, Gygi et al, Anderson et al and Chen et al which rely upon factual experimental data. As such, without evidence particular to the claimed protein, variants and fragments and in view of the relied upon teachings of Haynes et al, the second declaration of Dr. Grimaldi is still not persuasive. Haynes et al, Gygi et al, Chen et al and Anderson et al does in fact refute and rebut the opinion and conclusions of Dr. Grimaldi. The same position is taken with respect to the declaration of Dr. Polakis. Haynes et al and Gygi et al establish that there is no strong correlation of mRNA levels with protein levels and specifically conclude that protein levels cannot be accurately predicted from mRNA levels. Dr. Polakis does not provide any evidence to support his opinion and does not provide any evidence with any particularity to the claimed polypeptide. The declaration by Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding levels of the encoded protein. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor makers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma that in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes reports of instances where such a correlation does not exist, as exceptions to the rule. This has been full considered but is not found to be persuasive. The

declaration does not provide data such that the examiner can independently draw conclusions, or provide any objective evidence with respect to the instantly claimed polypeptides. Only, Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Further, while the declaration may allege (no evidence is presented) that there is a correlation between mRNA expression and protein over-expression in some cases, Applicants have presented no objective evidence that the claimed PRO polypeptide or any variant thereof is overexpressed as asserted, relative to normal cells. Applicants draw different conclusions than specifically recited in Haynes et al and Gygi et al. The opinion of the declarations of Dr Grimaldi and Dr Polakis are in contrast to the conclusions of Haynes et al, Gygi et al, Chen et al and Anderson et al of record which are based in factual evidence. Therefore, in the absence of specific particular evidence to the contrary directed to the claimed polypeptides, the evidence of record is deemed to properly rebut and question the accuracy of the opinions of Dr. Grimaldi and Polakis in the respective declarations. The declarations, in contrast to Applicants position, did not provide any evidence or facts. Applicants argue that the revised interim guidelines establish that proteins that are differentially expressed in cancer have utility for diagnosis. This is not persuasive, it remains to be established that the claimed proteins are differentially expressed. Applicants argue that Alberts et al (1994) establish that for most genes transcriptional control is predominant. This is not persuasive, Hanyes et al and Gygi et al specifically refute the dogma and indicate that in contrast to the state of the art in 1994, it is recognized that the "multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products and reveal their correct identities and amounts." This was the state of the art in 1998. The broad sweeping conclusions of the art are not supported by careful evaluation and study of Haynes et al and Gygi et al. Applicants argue Zhigang et al that established as correlation

of mRNA production and protein production in diagnosis and treatment of human prostate cancer. Zhigang et al does what applicants have not done for SEQ ID NO:51 or 52, a mRNA and protein analysis in multiple samples to establish such a correlation that is statistically significant and relevant. Zhigang et al is not persuasive in view of Hanyes et al and Gygi et al of record, which establish that for any random mRNA there is no "more likely than not" standard with protein amounts. Applicants argue that the fundamental principal of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells and cite Meric et al. While this may be true, Hu et al teach that small differences in levels of mRNA does not predict any role in cancer formation or generation and therefore it is not understood how such a finding can be used for cancer therapeutics as asserted is supported by Meric et al, nor has such been established for the nucleic acid of SEQ ID NO:51 or the polypeptide of SEQ ID NO:52. The differences in transcript levels or protein levels have not been reported in the specification and the specification does not teach how to use such in therapeutics of cancer. Therefore, this specification fails to establish a role for SEQ ID NO:51 or 52 in carcinogenesis or tumor suppression. Applicants review the declaration of Dr. Ashkenazi that teaches that in situations where protein overexpression does not parallel gene amplification in certain tumor cell types but not others, the protein enables more accurate tumor classification and hence better determination of therapy which is a utility. This is not persuasive, such is not a contemplated utility of the specification and even if it was, there is no teaching of how to perform the asserted use for classification or determination of therapy for any cancer. Applicants hypothesize that if the gene is amplified but not the corresponding protein, then the clinician accordingly will decide not to treat a patient with agents that target that gene product. This argument fundamentally flawed, the specification does not teach agents that target the gene product (i.e. the instantly claimed polypeptides) and therefore how could any clinician make any choice of tumor classification and therapy options based on this specification.

Applicants continue to maintain that differential expression is that which provides for utility of the present invention. However, it is maintained that mRNA levels are not reasonably predictive of protein levels and the state of the art in 1998 provides evidence that substantiates that conclusion. Applicants have not provided any evidence in particular to the claimed invention and instead seek to establish that at the time that the invention was made that it protein expression more likely than not followed mRNA levels. This is not persuasive for all the reasons made of record. Applicants argue that Hanna et al supports the position of Dr. Ashkenazi that indicates therapy is chosen based on the presence or absence of the Her-2/neu protein. This is not persuasive, in this case the protein is overexpressed in normal, not in cancer cells and Hanna et al along with the art cited therein have clearly and unambiguously taught a biological role for Her-2/neu in certain breast cancers. This specification is devoid of such information with respect to the antibody that binds the protein of SEQ I DNO:52 and any cancer. Applicants assert that Konapka et al provides evidence of the correlation of mRNA levels with protein levels. This is not persuasive, Konopka et al makes no such generalization and in contrast the teachings of Haynes et al and Gygi et al make general conclusions opposite to that provided by Applicants. Applicants again argue a presumption of utility and no need to absolutely prove the asserted utility is real and only evidence needs to be reasonable indicative of the asserted utility. This is not persuasive, for all the reasons previously set forth. Haynes et al, Gygi et al, Anderson et al and Chen et al establish that the evidence is not reasonable indicative, nor "more likely than not". Applicants argue that the PTO has not provided a *prima facie* case, and even if it had the submitted evidence and declarations are sufficient to overcome the prima facie case. It is maintained a *prima facie* case has been established and that the proffered evidence is insufficient to obviate the *prima facie* case of lack of utility for the protein. Applicants argue that the declaration of Dr. Grimaldi establishes that the data in Example 18 are real and significant. This again is not persuasive for all the reasons made of record. Applicants again argue that it is well

established in the art that a change in mRNA levels heralds the same change in protein levels. This is not persuasive, the art of record specifically teaches that the two are not more likely than not linked, nor meets the "more likely than not" in view of the teachings of Haynes et al and Gygi et al of record. The assertion of a diagnostic is not found to be substantial. There is no evidence that the claimed polypeptides are differentially expressed and that such expression is statistically significant across multiple samples as is requisite for a diagnostic utility. Applicants argue the standard of clear inoperability for the entire claims and if it is minimally useful for achieving a useful result a rejection of the claimed invention is not warranted. This is not persuasive. No minimally useful result has been provided with respect to the claimed protein(s). In view of the totality of the record, the lack of any particulars with respect to the claimed polypeptides, the teachings of Haynes et al, Gygi et al, Anderson et al and Chen et al, it is found that that it is not reasonable to conclude that protein levels can be predicted from mRNA levels. In summary, the instant specification provides a mere invitation to experiment for establishing a specific and substantial use for the claimed antibodies that bind the polypeptide of SEQ ID NO:52, which does not reasonably extrapolate to a readily available utility for all the reasons made of record. The rejection is maintained.

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention is maintained for reasons made of record in the previous Office Action mailed 8-23-05.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Barnes (WO 00/18904, published 06 April 2000) is maintained for reasons made of record in the Office Action mailed 8-23-05.

Applicants argue the the reference is not a 102(b) reference because it was not published more than 1 year before the priority date of the instant application, which applicants assert is either August 24, 2000 (the filing dagte of PCT/US00/23328) or the July 2, 1998 provisional application 60/091,628. This is not persuasive, in order to be accorded priority under 35 USC 120 or 119(e), the earlier filed applications must comply with all the provisions of 35 USC 112, first pargraph. The position of the office is that neither the instant application nor any of the earlier filed applications has utility for the claimed antibodies for all the reasons made of record. As such, priority is not accorded to the earlier filed applications and the rejection is maintained.

Status of Claims

All claims stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Pat a. Duffy

Patricia A. Duffy

Primary Examiner

Art Unit 1645